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In this issue:

A BRIEF INTRODUCTION TO GENETICS RESEARCH IN PTSD

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On April 14, 2003, the International Human Genome Sequencing Consortium, led in the United States by the National Human Genome Research Institute (NHGRI) and the Department of Energy, announced that the human genome had been sequenced. With the Human Genome Project complete, NHGRI has outlined its vision for the future of genetics research (Collins et al., 2003). A major new focus is the development of tools to identify genes that contribute to common, complex disorders including mental disorders such as PTSD. As we are entering the "era of the genome," the time has come for considering the current state of the literature on the genetics of PTSD.

From the vantage point of genetics research, PTSD is considered a complex or polygenetic disorder. Unlike Huntington's disease and other disorders that are caused by a single gene, there is likely no "PTSD gene" that is necessary and sufficient for the development of the disorder. Instead, there are probably many different genes, each of which contributes interchangeably and additively, in a probabilistic fashion, to the inherited liability for PTSD.

Genetics research in PTSD has followed a logical series of steps, similar to that of genetics research on other disorders. First, family studies were conducted. If PTSD is genetic, family members of individuals with PTSD should have a higher prevalence of PTSD. PTSD prevalence should be higher in first-degree relatives (parents, siblings, children) than second- or third-degree relatives because first-degree relatives share more of their genes. Next, twin studies have shown the relative magnitude of genetic and environmental influences on individual differences in trauma exposure and PTSD. More recently, candidate gene association studies have sought to identify specific genes that increase risk of PTSD.

Family studies. There are two main methods for conducting family studies: the family history method and the family study method. Both methods begin by selecting cases and controls, which are called probands in genetic studies. The family history method collects psychiatric information about all family members by interviewing the proband. Family history studies are conducted using instruments designed for this purpose such as the Family Interview for Genetic Studies (FIGS). The family study method, on the other hand, interviews all family members directly using an instrument such as the Diagnostic Interview for Genetic Studies (DIGS). Family studies of PTSD have primarily used some variation of the family history method. The family history method has several well-documented limitations. Overall, family history studies tend to underestimate the prevalence of mental disorders in relatives. Moreover, proband reports of diagnostic status in relatives are influenced by their own history of psychopathology (Khoury et al., 1993).

Compared with other disorders, such as major depression, relatively few family studies of PTSD have been conducted. Most evidence for the role of familial risk factors in PTSD comes from epidemiological studies. The results of such studies are contradictory. Moreover, most suggest familial psychopathology increases risk of both trauma exposure and PTSD, although the mechanism by which this occurs is unclear. A family history of psychopathology could increase risk of PTSD directly or indirectly. In my own study of familial risk factors for PTSD, I found that a family history of conduct disorder, major depression, panic disorder or GAD, and substance dependence were each significantly associated with PTSD. However, this association is indirect, mediated by increased risk of trauma exposure and pretrauma psychopathology (Koenen et al., 2002).

Only a few family studies have specifically examined whether relatives of PTSD probands have an increased prevalence of PTSD. In one such study, Sack and colleagues (1995) compared the prevalence of PTSD in Cambodian refugee children whose parents had PTSD with the prevalence in refugee children whose parents did not develop PTSD. When compared to children whose parents did not have PTSD, children whose mothers or fathers had PTSD were almost five times more likely to receive the diagnosis. Similar findings have been shown in a series of studies on adult children of Holocaust survivors with PTSD. Results of this work show that these children have a higher risk of PTSD following trauma exposure than adult children of Holocaust survivors without PTSD (Yehuda et al., 1998; Yehuda et al., 2001).

One difficulty for family studies of PTSD is that the disorder cannot be assessed in relatives who have not experienced a traumatic event. Since it is unknown whether these relatives would have developed PTSD had they been exposed, information on PTSD diagnostic status for such relatives must be treated as missing data. To get around this problem, several family studies have examined whether

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relatives of individuals with PTSD show higher rates of other mental disorders than relatives of individuals without PTSD. Such studies enable investigators to examine whether PTSD has a familial relationship with another disorder. Davidson and colleagues (1998) used this approach in a family study of chronic rape-related PTSD. The study included five groups of probands: female rape survivors with lifetime PTSD, rape survivors without lifetime PTSD, major depressive disorder controls, anxiety disorder controls, and healthy controls. Data on psychiatric status was collected directly from first-degree family members, and family history data was collected from probands. The findings showed no association between a family history of anxiety disorder or substance abuse and PTSD. An association between a family history of major depression and PTSD was found. However, this association was limited to probands with PTSD who also had lifetime major depression. The results of this study do not support the hypothesis that PTSD, on its own, has a familial relationship with any of the assessed disorders. Other family studies have found elevated prevalences of mental disorders in relatives of PTSD probands (Davidson et al., 1985; Reich et al., 1996). The most consistent finding has been a family history of anxiety in relatives of PTSD probands as compared to combat controls (Davidson et al., 1989).

Twin studies. Family studies are limited in that they cannot determine whether a disorder runs in families due to shared genes or shared environment. The twin method has been used to disentangle the role of genetic and family-wide environmental influences on risk for PTSD. The basic twin method compares the degree of similarity within identical or monozygotic (MZ) pairs with the degree of similarity within fraternal or dizygotic (DZ) pairs. MZ twins share 100% of their genes and 100% of the family environment; DZ twins share on average 50% of their genes and 100% of the family environment. If MZ twins are significantly more similar on a characteristic than DZ twins, then this characteristic is interpreted as being genetically influenced. Since both MZ and DZ twins share 100% of the family environment, the higher degree of similarity between MZ twins must be due to genetic factors. Twin studies are used to calculate heritability or the proportion of the variance in a trait or condition due to genetic factors. The heritability estimate is derived by $2(r_{mz} - r_{dz})$, where r = the intraclass twin correlation (Plomin et al., 2000). For categorical phenotypes, such as PTSD diagnosis, the tetrachoric correlation, which assumes an underlying normal distribution of liability, is used to calculate heritability. It is important to note, however, that the twin model depends on several assumptions, including additivity, equal environments, and no assortative mating. Plomin et al. provides a clear and thoughtful overview of the twin method, related assumptions, and relevant findings for mental disorders.

Twin studies provide the strongest evidence thus far for genetic influences on risk for both trauma exposure and PTSD. The majority of such studies have been based on data from the Vietnam Era Twin (VET) Registry, which consists of male-male twin pairs who served in the military during the Vietnam era and was created from military records. Genetic influences explained 47% of the variance in combat exposure in VET Registry twin pairs who served in Vietnam (Lyons et al., 1993). Substantial genetic influences were also found on all PTSD symptoms, after adjusting for differences in combat exposure (True et al., 1993). Further studies on the VET Registry have shown that there are shared genetic influences on PTSD and other mental disorders, including alcohol and drug dependence (McLeod et al., 2001; Xian et al., 2000), generalized anxiety and panic disorder symptoms (Chantarujikapong et al., 2001), and major depression (Koenen et al., 2003). Recently, work by Stein and colleagues (2002) has demonstrated similar findings in a non-veteran volunteer community sample of male and female twins. Their study found that exposure to assaultive violence (e.g., rape, combat, physical assault) and PTSD symptoms were both moderately heritable.

Association studies. The association method can detect genes of small effect and is therefore the method of choice for molecular genetic studies of complex disorders (Risch & Merikangas, 1996; Tabor et al., 2002; Sullivan et al., 2001). Humans are 99.9% genetically identical. Research aimed at identifying genes that explain individual differences in risk for PTSD, therefore, focuses on the tiny fraction of DNA that differs among individuals. Association studies correlate a DNA marker's alleles, which are different forms of DNA at a specific place (or locus) on the chromosome, with an outcome. Alternatively, association studies can focus on endophenotypes or markers of the neurobiological pathways thought to mediate the relationship between the gene and the disorder. For example, Radant et al. (2001) propose that genes involved in the endophenotypes of HPA axis dysregulation, physiology of hyperarousal, and acoustic startle response might influence the development of PTSD.

Candidate genes are selected where there is *a priori* evidence to hypothesize an association with the outcome of interest. The best candidates for study are functional polymorphisms or genetic variants that have been shown to impact neurobiological pathways implicated in the outcome. Since our genetic code is very similar to that of other mammals, animal studies often suggest potential candidates for human genetic studies. For example, King et al. (2001) have proposed congenital learned helplessness as a potential animal model for the genetics of PTSD. Genes found to influence variation in animal models of learned helplessness present potential candidates for future association studies of PTSD.

Only four association studies of PTSD have been published, all of which focused on candidate genes involved in the dopaminergic system. Findings from these studies are conflicting. Three of the studies examined the association between marker alleles at the D_2 dopamine receptor gene (DRD2) and PTSD, with conflicting results. The first study found a positive association with the DRD_2A1 allele (Comings et al., 1996). The second study found no association with the DRD_2A1 allele or with any single allele

or combination of alleles for the DRD2 locus (Gelernter et al., 1999). The third study found a positive association between DRD_2A1 and PTSD only in the subset of PTSD cases that engaged in harmful drinking (Young et al., 2002). The fourth study, by Segman et al. (2002), found a positive association between the dopamine transporter SLC6A3 3' variable number tandem repeat polymorphism and PTSD.

Of the four studies, that by Segman et al.(2002) presents the strongest evidence for an association between genetic variants involved in the dopaminergic system and PTSD. The three prior studies shared several limitations, including limited power due to small sample and comorbid substance abuse in probands. Furthermore, the studies by Gelernter et al. (1999) and Young et al. (2002) failed to assess trauma exposure in controls. Since genetic liability for PTSD can only be expressed in the presence of exposure, this would bias these studies against finding an association. That is, although the controls do not have PTSD, they could have the genetic liability for the disorder and potentially would have developed it had they been exposed. Thus, including unexposed controls potentially makes the control genetically more similar to the cases. Future association studies of PTSD should follow the lead of Segman et al. and use trauma-exposed controls.

Interpreting the data. We are still in the early stages of research on the genetics of PTSD. Family studies of PTSD have been limited methodologically and provided conflicting findings. As of this writing, no family study of PTSD has obtained complete pedigrees through the family study method. It is difficult to draw conclusions, therefore, about the presence of a familial relationship between PTSD and other mental disorders. Twin studies provide strong evidence for the heritability of PTSD. However, these studies have not distinguished between genetic influences on trauma exposure versus PTSD. Nor have they examined whether the heritability of PTSD varies with the type or severity of trauma exposure. Such data would be informative in selecting probands for association studies. Future association studies could potentially benefit from conceptualizing the genetics of PTSD from pursuing methodologically rigorous designs. The articles by Sullivan et al. (2001) and Tabor et al. (2002) provide important recommendations for the design and conduct of association studies.

REFERENCES

COLLINS, F.S., GREEN, E.D., GUTTMACHER, A.E., & GUYER, M.S. (2003). **A vision for the future of genomics research.** *Nature, 422*, 835-847.

KHOURY, M.J., BEATY, T.H., & COHEN, B.H. (1993). *Fundamentals of genetic epidemiology.* New York: Oxford University Press.

PLOMIN, R., DEFRIES, J.C., MCCLEARN, G.E., & MCGUFFIN, P. (2000). *Behavioral genetics (4th ed.).* San Francisco: W.H. Freeman.

RISCH, N., & MERIKANGAS, K. (1996). **The future of genetic studies of complex human diseases.** *Science, 273*, 1516-1517.

SULLIVAN, P. F., EAVES, L. J., KENDLER, K. S., & NEALE, M.C. (2001). **Genetic case-control association studies in neuropsychiatry.** *Archives of General Psychiatry, 58*, 1015-1024.

TABOR, H. K., RISCH, N. J., & MYERS, R. M. (2002). **Candidate-gene approaches for studying complex genetic traits: Practical considerations.** *Nature Reviews. Genetics, 3*, 391-397.

WEBSITES

Behavioural Genetics Interactive Modules (Author: S. Purcell)
http://statgen.iop.kcl.ac.uk/bgim/

Behavior Genetics Links Page (Author: M. Miller)
http://taxa.epi.umn.edu/~mbmiller/306/2000fs/bglinks.htm

Diagnostic and Family Interviews for Genetic Studies (Author: NIMH) (FIGS, DIGS 2.0, DIGS 3.0/B)
http://zork.wustl.edu/nimh/digs/newpage11.htm

Human Genome Project
http://www.ornl.gov/TechResources/Human_Genome/

LocusLink
http://www.ncbi.nlm.nih.gov/LocusLink/

Mx Statistical Modeling (Author: Michael Neale)
http://www.vcu.edu/mx/

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http://www3.ncbi.nlm.nih.gov/Omim/

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http://statgen.iop.kcl.ac.uk/summerschool/

Institute of Behavioral Genetics, University of Colorado, Boulder, CO, USA
http://ibgwww.colorado.edu/

SELECTED ABSTRACTS

CHANTARUJIKAPONG, S.I., SCHERRER, J.F., XIAN, H., EISEN, S.A., LYONS, M.J., GOLDBERG, J., TSUANG, M.T., & TRUE, W.R. (2001). **A twin study of generalized anxiety disorder symptoms, panic disorder symptoms and post-traumatic stress disorder in men.** *Psychiatry Research, 103,* 133-145. Generalized anxiety disorder (GAD), panic disorder (PD) and PTSD often co-occur. We investigated whether and to what degree genetic and environmental contributions overlap among symptoms of GAD, symptoms of PD, and PTSD. Subjects were 3327 monozygotic and dizygotic male-male twin pair members of the Vietnam Era Twin Registry who participated in a 1992 telephone administration of the Diagnostic Interview Schedule Version 3 Revised (DIS3R). Genetic model fitting was performed to estimate the magnitude of genetic and environmental contributions to the lifetime co-occurrence of GAD symptoms, PD symptoms, and PTSD. The liability for GAD symptoms was due to a 37.9% additive genetic contribution common to PD symptoms and PTSD. Liability for PD symptoms was due to a 20.7% additive genetic contribution common to GAD symptoms and PTSD, and a 20.1% additive genetic influence specific to PD symptoms. Additive genetic influences common to symptoms of GAD and PD accounted for 21.3% of the genetic variance in PTSD. Additive genetic influences specific to PTSD accounted for 13.6% of the genetic variance in PTSD. Remaining variance for all three disorders was due to unique environmental factors both common and specific to each phenotype. These results suggest that these disorders each have etiologically distinct components and also have significant genetic and unique environmental contributions in common.

COMINGS, D.E., MUHLEMAN, D., & GYSIN, R. (1996). **Dopamine D_2 receptor (DRD2) gene and susceptibility to posttraumatic stress disorder: A study and replication.** *Biological Psychiatry, 40,* 368-372. Subjects on an addiction treatment unit who had been exposed to severe combat conditions in Vietnam were screened for PTSD. Of 24 with PTSD, 58.3% carried the D_2A1 allele. Of the remaining 8 who did not meet PTSD criteria, 12.5% carried the D_2A1 allele ($p = 0.04$). In a replication study of 13 with PTSD, 61.5% carried the D_2A1 allele. Of the remaining 11 who did not meet criteria for PTSD, 0% carried the D_2A1 allele ($p = 0.002$). For the combined group 59.5% of those with PTSD carried the D_2A1 allele versus 5.3% of those who did not have PTSD ($p = 0.0001$). These results suggest that a DRD_2 variant in linkage disequilibrium with the D_2A1 allele confers an increased risk to PTSD, and the absence of the variant confers a relative resistance to PTSD.

DAVIDSON, J., SMITH, R., & KUDLER, H. (1989). **Familial psychiatric illness in chronic posttraumatic stress disorder.** *Comprehensive Psychiatry, 30,* 339-345. 108 veterans with PTSD were compared with 60 age-matched controls with regard to family history of psychiatric illness. Depressed controls had a higher morbidity risk (MR) for depression and generalized anxiety in siblings/parents and children, respectively. Patients with PTSD did not differ from alcoholics or nonpsychiatric controls on the basis of family history. PTSD was associated with greater familial anxiety when compared with controls who had experienced combat. When World War II and Vietnam veterans with PTSD were compared, a higher MR for alcohol and drug abuse was found in siblings/parents of Vietnam veterans, and a higher MR was found for other chronic psychiatric disorders in the children of Vietnam veterans.

DAVIDSON, J., SWARTZ, M., STORCK, M., KRISHNAN, R.R., & HAMMETT, E. (1985). **A diagnostic and family study of posttraumatic stress disorder.** *American Journal of Psychiatry, 142,* 90-93. A family history study of 36 patients with chronic PTSD revealed a positive history of familial psychopathy in 66% of the patients. Alcoholism, depression, and anxiety disorders were the disorders most commonly found. The patients also had a higher prevalence of alcoholic siblings than did a retrospectively derived control group of depressed and anxious male patients. With respect to the proportion of familial anxiety to familial depression, the probands with PTSD more closely resembled probands with generalized anxiety than probands with depression. Every patient had experienced at least one significant psychiatric illness during his lifetime, most commonly alcohol abuse or depression.

DAVIDSON, J.R.T., TUPLER, L.A., WILSON, W.H., & CONNOR, K.M. (1998). **A family study of post-traumatic stress disorder following rape trauma.** *Journal of Psychiatric Research, 32,* 301-309. There is evidence that familial factors serve as determinants of risk for PTSD, especially familial anxiety. This study investigates the relationship between chronic PTSD and family psychiatric morbidity. The sample was drawn from 81 female rape survivors with or without lifetime PTSD, 31 major depressive disorder controls, 20 anxiety disorder controls and 39 healthy controls. First-degree family members were directly interviewed ($n = 285$) and diagnoses assigned of major depressive, anxiety and alcohol or substance use disorder. Information was also available by family history for 639 relatives. In the directly interviewed sample, no consistently increased morbidity risk was observed for anxiety in healthy control groups. When comorbid depression in rape survivor probands was taken into account post hoc, an increased risk for depression was noted in family members of PTSD probands with depression, but not in relatives of PTSD probands without lifetime depression. Among rape survivor probands with non-comorbid PTSD, rates by history of familial anxiety and depression were negligible. In a logistic regression analysis, individual vulnerability to depression served as an independent predictor of chronic PTSD, along with specific trauma-related variables. In the family history group, results were consistent with those obtained from the directly interviewed group. Our findings clearly support the view that PTSD following rape is associated with familial vulnerability to major depression, which may thus serve as a risk factor for developing PTSD. The exact nature of this predisposition calls for further inquiry and there is a need to expand this study to include other PTSD populations. PTSD may on occasion represent a form of depression which is induced and/or modified neurobiologically and phenomenologically by extreme stress. Our findings may be a reflection of the sample composition, the current conceptualization of PTSD, or be related to study limitations.

GELERNTER, J., SOUTHWICK, S., GOODSON, S., MORGAN, A., NAGY, L., & CHARNEY, D.S. (1999). **No association between D_2 dopamine receptor (DRD2) "A" system alleles, or DRD2 haplotypes, and posttraumatic stress disorder.** *Biological Psychiatry, 45,* 620-625. *Background:* Association studies between marker alleles at the D_2 dopamine receptor gene (DRD2) and various psychiatric illnesses have produced conflicting results. Reports of allelic associations were originally made with alcoholism, but were then extended to other psychiatric disorders, including PTSD. *Methods:* We studied allele frequency of the DRD2 TaqI "A," "B," and "D" system markers in 52 European-American subjects with diagnoses of PTSD (based on structured

interviews). *Results:* Frequency of the A1 allele in this sample was .15, not significantly different from the .19 allele frequency seen in 87 control subjects. We were thus unable to replicate the previous reports of allelic association between the DRD2 TaqI "A1" allele and PTSD. There were also no significant differences in allele frequency for the "B" or "D" systems. We then computed three marker (TaqI "A," "B," and "D" system) haplotypes for the sample; DRD2 haplotype frequencies also did not differ between control subjects and subjects with PTSD. *Conclusions:* We conclude that DRD2 alleles are not associated with PTSD in this sample, and that genetic variation at the DRD2 locus is not likely to be an important contributor to risk for this disorder.

KOENEN, K.C., HARLEY, R., LYONS, M.J., WOLFE, J., SIMPSON, J.C., GOLDBERG, J., EISEN, S.A., & TSUANG, M.T. (2002). **A twin registry study of familial and individual risk factors for trauma exposure and posttraumatic stress disorder.** *Journal of Nervous and Mental Disease*, *190*, 209-218. This study examines the association of individual and familial risk factors with exposure to trauma and PTSD in male twins ($n = 6744$) from the Vietnam Era Twin Registry. Independent reports of familial psychopathology from co-twins were used to avoid the potential biases of the family history method. Risk for exposure to traumatic events was increased by service in Southeast Asia, preexisting conduct disorder, preexisting substance dependence, and a family history of mood disorders whose effects appear to be partly genetic. Preexisting mood disorders in the individual were associated with decreased odds of traumatic exposure. Risk of developing PTSD following exposure was increased by an earlier age at first trauma, exposure to multiple traumas, paternal depression, less than high school education at entry into the military, service in Southeast Asia, and preexisting conduct disorder, panic disorder or generalized anxiety disorder, and major depression. Results suggest the association of familial psychopathology and PTSD may be mediated by increased risk of traumatic exposure and by preexisting psychopathology.

KOENEN, K.C., LYONS, M.J., GOLDBERG, J., SIMPSON, J., WILLIAMS, W.M., TOOMEY, R., EISEN, S.A., TRUE, W.R., CLOITRE, M., WOLFE, J., & TSUANG, M.T. (2003). **A high risk twin study of combat-related PTSD comorbidity.** *Twin Research*, *6*, 218-226. Combat-related PTSD is highly comorbid with other mental disorders. However, the nature of the relationship between PTSD and other mental disorders remains unclear. A discordant high-risk twin design was used on the data from a sub-sample of the male-male twin pair members of the Vietnam Era Twin Registry to examine whether patterns of comorbidity are consistent with a psychopathological response to combat exposure or reflect familial vulnerability to psychopathology. Mental disorders were assessed via the Mental Health Diagnostic Interview Schedule Version III-Revised. Discordant monozygotic within-pair comparisons revealed that PTSD probands had higher symptom counts and diagnostic prevalences of mood and anxiety disorders than their non-combat exposed co-twins. Monozygotic co-twins of PTSD probands had significantly more mood disorder symptoms than monozygotic co-twins of combat controls or dizygotic co-twins of veterans with PTSD. These findings suggest that a) major depression, generalized anxiety disorder and panic disorder are part of a post-combat response syndrome; b) a shared familial vulnerability also contributes to the association between PTSD and major depression, PTSD and dysthymia, and c) this shared vulnerability is mediated by genetic factors.

LYONS, M.J., GOLDBERG, J., EISEN, S. A., TRUE, W., TSUANG, M. T., MEYER, J. M., & HENDERSON, W.G. (1993). **Do genes influence exposure to trauma? A twin study of combat.** *American Journal of Medical Genetics*, *48*, 22-27. Data from 4,029 male-male twin pairs who served in the United States military during the Vietnam era (1965-1975) were used to examine genetic and non-genetic factors that influence wartime exposure to traumatic events. Specific events examined were volunteering for service in Vietnam, actual service in Southeast Asia, a composite index of 18 combat experiences, and information from military records about being awarded combat decorations. Correlations within monozygotic (MZ) and dizygotic (DZ) twin pairs for volunteering for service in Vietnam were 0.40 and 0.22, respectively. For actually serving in Southeast Asia, the MZ correlation was 0.41 and the DZ correlation was 0.24. Analysis of twin pairs in which both siblings served in Southeast Asia ($n = 820$) demonstrated a correlation for self-reported combat experiences within MZ and DZ pairs of 0.53 and 0.30, respectively. Heritability estimates ranged from 35 to 47%. The family environment did not have a significant effect on any of the variables. Analyses of data from military records regarding being awarded a combat decoration provided very similar results to those found for self-reported combat experiences.

REICH, J., LYONS, M., & CAI, B. (1996). **Familial vulnerability factors to post-traumatic stress disorder in male military veterans.** *Acta Psychiatrica Scandinavica*, *93*, 105-112. The question has been frequently raised about whether there are emotional disorders that predispose to PTSD. We do know that those with PTSD do have many comorbid disorders, but due to the difficulty in performing prospective studies it is hard to tell what is cause and what is effect. This study bypassed the problem caused by comorbidity by examining family history of 4 proband groups: PTSD, mixed anxiety disorders, coexisting anxiety and depressive disorders, and screened normal controls. 2 questions were examined. First, whether family history predicted who experienced combat situations and second, whether the proband groups could be distinguished by family history. Logistic regression identified 2 variables that predicted the experience of combat: major depression (odds ratio = 2.17) and the DSM-III dramatic personality disorder cluster (odds ratio = 1.36). Although there was considerable overlap, family history variables distinguished PTSD from other proband groups. Overall, the pattern of psychopathology in the families of the PTSD probands most closely resembled that in the families of the coexisting anxiety and depressive disorders probands. We conclude that family history methods may be an addition to possible variables that predict who will be exposed to combat and also that family history variables may be able to distinguish a PTSD population from some other types of emotional disorders.

SACK, W.H., CLARKE, G.N., & SEELEY, J. (1995). **Posttraumatic stress disorder across two generations of Cambodian refugees.** *Journal of the American Academy of Child and Adolescent Psychiatry*, *34*, 1160-1166. *Objective:* To examine the expression of war-related trauma as manifested by DSM-III-R rates of PTSD and major depressive disorder in two generations of Cambodian refugees living in the western United States. *Method:* A probability sample of 209 Khmer adolescents and one of their parents were interviewed using portions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version and the PTSD section of the Diagnostic Interview for Children and Adolescents. Interviews were conducted in English

by a master's-level clinician with a Khmer interpreter. *Results:* PTSD was found to be significantly related across parent-child generations. A nonsignificant generational trend was also found for depressive disorders. A number of environmental variables measured in the study (amount of reported war trauma, loss, living arrangements, treatment received, socioeconomic status) were not related to these findings. Parents were more likely to report an earlier onset of PTSD symptoms. *Conclusions:* This study suggests that PTSD in refugees may cluster in families. Whether this phenomenon is caused by a genetic susceptibility to trauma awaits further research. PTSD and depressive disorders in refugee populations, while often comorbid, appear to follow different courses over time.

SEGMAN, R.H., COOPER-KAZAZ, R., MACCIARDI, F., GOLTSER, T., HALFON, Y., DOBROBORSKI, T., & SHALEV, A.Y. (2002). **Association between the dopamine transporter gene and posttraumatic stress disorder.** *Molecular Psychiatry, 7,* 903-907. PTSD is a chronic anxiety disorder that follows exposure to extreme events. A large twin study of Vietnam veterans had demonstrated a significant genetic contribution to chronic PTSD upon exposure to combat. The underlying genes, however, have not been described. Given previous findings of abnormal dopamine (DA) function in PTSD, and given the putative effect of dopamine neurotransmission in shaping the responses to stress in animals, this study examined the association of the dopamine transporter (DAT) SLC6A3 3' variable number tandem repeat (VNTR) polymorphism with PTSD. The study evaluated 102 chronic PTSD patients and 104 carefully-documented trauma survivors (TS) who did not develop PTSD. Significant excess of 9 repeat allele was observed among PTSD patients (43% vs. 30.5% in TS controls; $\chi_2 = 6.3$, $df = 1$, $p = 0.012$). An excess of 9 repeat homozygous genotype was also observed in PTSD (20.43% in PTSD vs 9.47% in TS controls; $\chi_2 = 6.11$, $df = 2$, $p < 0.047$). These findings suggest that genetically determined changes in dopaminergic reactivity may contribute to the occurrence of PTSD among trauma survivors.

STEIN, M.B., JANG, K.L., TAYLOR, S., VERNON, P.A., & LIVESLEY, W.J. (2002). **Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: A twin study.** *American Journal of Psychiatry, 159,* 1675-1681. *Objective:* PTSD develops in only a subset of persons exposed to traumatic stress, suggesting the existence of stressor and individual differences that influence risk. In this study the authors examined the heritability of trauma exposure and PTSD symptoms in male and female twin pairs of nonveteran volunteers. *Method:* Scores on a traumatic events inventory and a DSM-IV PTSD symptom inventory were examined in 222 monozygotic and 184 dizygotic twin pairs. Biometrical model fitting was conducted by using standard statistical methods. *Results:* Additive genetic, common environmental, and unique environmental effects best explained the variance in exposure to assaultive trauma (e.g., robbery, sexual assault), whereas exposure to nonassaultive trauma (e.g., motor vehicle accident, natural disaster) was best explained by common and unique environmental influences. PTSD symptoms were moderately heritable, and the remaining variance was accounted for by unique environmental experiences. Correlations between genetic effects on assaultive trauma exposure and on PTSD symptoms were high. *Conclusions:* Genetic factors can influence the risk of exposure to some forms of trauma, perhaps through individual differences in personality that influence environmental choices. Consistent with symptoms in combat veterans, PTSD symptoms after noncombat trauma are also moderately heritable. Moreover, many of the same genes that influence exposure to assaultive trauma apear to influence susceptibility to PTSD symptoms in their wake.

TRUE, W. J., RICE, J., EISEN, S.A., HEATH, A.C., GOLDBERG, J., LYONS, M.J., & NOWAK, J. (1993). **A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms.** *Archives of General Psychiatry, 50,* 257-264. We studied 4042 Vietnam era veteran monozygotic and dizygotic male twin pairs (from the Vietnam Era Twin Registry) to determine the effects of heredity, shared environment, and unique environment on the liability for 15 self-reported PTSD symptoms included in the symptom categories of reexperiencing the trauma, avoidance of stimuli related to the trauma, and increased arousal. Quantitative genetic analysis reveals that inheritance has a substantial influence on liability for all symptoms. Symptoms in the reexperiencing cluster and one symptom in the avoidance and numbing cluster are strongly associated with combat exposure, and monozygotic pairs are more highly concordant for combat exposure than dizygotic pairs. By fitting a bivariate genetic model, we show that there are significant genetic influences on symptom liability, even after adjusting for differences in combat exposure; genetic factors account for 13% to 30% of the variance in liability for symptoms in the reexperiencing cluster, 30% to 34% for symptoms in the avoidance cluster, and 28% to 32% for symptoms in the arousal cluster. There is no evidence that shared environment contributes to the development of PTSD symptoms.

YEHUDA, R., HALLIGAN, S.L., & BIERER, L.M. (2001). **Relationship of parental trauma exposure and PTSD to PTSD, depressive and anxiety disorders in offspring.** *Journal of Psychiatric Research, 35,* 261-270. This study examined the relationship of parental trauma exposure and PTSD to the development of PTSD, depressive, and anxiety disorders in the adult offspring of Holocaust survivors. 135 subjects (55 men and 80 women) were divided into three groups according to parental trauma exposure and PTSD: 60 subjects were offspring of Holocaust survivors who endorsed having at least one parent with PTSD, 33 were offspring of Holocaust survlvors who reported having no parent with PTSD, and 42 were demographically similar subjects with no parental Holocaust exposure. All subjects underwent a comprehensive psychiatric interview in which information about lifetime psychiatric diagnoses and exposure to traumatic events was obtained. Subjects also completed a checklist based on the 17 DSM-IV symptoms of PTSD, to estimate the symptom severity of PTSD in their parents. A presumptive diagnosis of parental PTSD was assigned according to DSM-IV criteria. Forward and forced entry stepwise logistic regression analyses were used to determine the effects of parental exposure, parental PTSD, and the subject's own history of trauma in the development of PTSD, depressive, and anxiety disorders in the offspring. The findings demonstrate a specific association between parental PTSD and the occurrence of PTSD in offspring. Additionally, parental trauma exposure, more than parental PTSD, was found to be significantly associated with lifetime depressive disorder. The identification of parental PTSD as a risk factor for PTSD in offspring of Holocaust survivors defines a sample in which the biological and psychological correlates of risk for PTSD can be further examined.

YOUNG, R. M., LAWFORD, B. R., NOBLE, E. P., KANN, B., WILKIE, A., RITCHIE, T., ARNOLD, L., & SHADFORTH, S. (2002). **Harmful drinking in military veterans with post-traumatic stress disorder: Association with the D2 dopamine receptor A1**

allele. *Alcohol & Alcoholism, 37,* 451-456. *Aims:* The frequency of the Taq I A alleles (A1 and A2) of the D2 dopamine receptor (DRD2) gene was examined in Caucasian PTSD patients and controls. *Results:* In 91 PTSD patients, the frequency of the A1 allele was higher ($p = 6.12 \times 10^{-3}$) than in the 51 controls. In the 38 PTSD harmful drinkers (>= 60 g alcohol / day), A1 allelic frequency was higher ($p = 3.91 \times 10^{-2}$) than in the 53 non-harmful drinkers (< 60 g alcohol / day), the former being also higher ($p = 3.76 \times 10^{-4}$) than in controls. However, there was no difference between non-harmful drinkers and controls. Based on DRD2 allelic association, the 35 PTSD patients with the A1(+) (A1A1, A1A2) allele consumed more than twice the daily amount of alcohol than the 56 patients with the A1(-) (A2A2) allele ($p = 1.94 \times 10^{-3}$). When the hourly rate of alcohol consumed was compared, A1(+) allelic patients consumed twice the rate of the A1(-) allelic patients ($p < 10^{-7}$). *Conclusion:* The DRD2 A1 allele was associated with PTSD. However, this association was found only in the harmful drinkers. PTSD patients with the A1(+) allele consumed more alcohol than patients with the A1(-) allele. The importance of determining alcohol consumption in DRD2 association studies with PTSD is suggested.

XIAN, H., CHANTARUJIKAPONG, S.I., SCHERRER, J.F., EISEN, S.A., LYONS, M.J., GOLDBERG, J., TSUANG, M.T., & TRUE, W.R. (2000). **Genetic and environmental influences on posttraumatic stress disorder, alcohol and drug dependence in twin pairs.** *Drug & Alcohol Dependence, 61,* 95-102. We investigated whether and to what degree genetic and environmental contributions overlap among PTSD, alcohol dependence (AD), and drug dependence (DD). Subjects were 3304 monozygotic and dizygotic male-male twin pair members of the Vietnam Era Twin Registry who participated in 1992 telephone administration of the Diagnostic Interview Schedule Version 3 Revised (DIS-3R). Genetic model fitting was performed to estimate the magnitude of genetic and environmental contributions to the lifetime co-occurrence of DSM-III-R PTSD, AD, and DD. The liability for PTSD was partially due to a 15.3% genetic contribution common to AD and DD and 20.0% genetic contribution specific to PTSD. Risk for AD was partially due to a 55.7% genetic contribution common to PTSD and DD. Genetic influences common to PTSD and AD accounted for 25.2% of the total risk for DD. Specific family environmental influence accounted for 33.9% of the total variance in risk for DD. Remaining variance for all three disorders was due to unique environmental factors both common and specific to each phenotype. These results suggest that PTSD, AD, and DD each have etiologically distinct components and also have significant genetic and unique environmental contributions in common.

ADDITIONAL CITATIONS
Annotated by the Editor

DIERKER, L.C. & MERIKANGAS, K.R. (2001). **Familial psychiatric illness and posttraumatic stress disorder: Findings from a family study of substance abuse and anxiety disorders.** *Journal of Clinical Psychiatry, 62,* 715-720.
Conducted a family study of 263 PTSD probands and 1206 of their adult first-degree relatives. The prevalence of PTSD was not elevated among family members of PTSD probands except in the subgroup of PTSD probands who also had alcoholism.

JANG, K.L., STEIN, M.B., TAYLOR, S., ASMUNDSON, G.J.G., & LIVESLEY, W.J. (in press). **Exposure to traumatic events and experiences: Aetiological relationships with personality function.** *Psychiatry Research.*
Assessed the relationship between personality and exposure to trauma in 222 monozygotic and 184 dizygotic twin pairs. Exposure to violent assaultive events was associated with antisocial personality traits. Genetic factors accounted for 5 to 11% of the observed relationship between personality and trauma exposure.

KING, J. A., ABEND, S., & EDWARDS, E. (2001). **Genetic predisposition and the development of posttraumatic stress disorder in an animal model.** *Biological Psychiatry, 50,* 231-237.
Developed a congenital animal model of learned helplessness in rats. Comparisons between the 33rd generations bred from helpless and nonhelpless strains showed that, following stressor exposure, the helpless strain had relatively higher pain tolerance, poorer memory performance, and a blunted cortisol response.

MCKENZIE, N., MARKS, I., & LINESS, S. (2001). **Family and past history of mental illness as predisposing factors in posttraumatic stress disorder.** *Psychotherapy and Psychosomatics, 70,* 163-165.
Examined family history of mental illness in 138 PTSD patients and 87 agoraphobics. In comparison with agoraphobics, PTSD patients were less likely to have a family history of anxiety disorder but not of mental disorder in general.

MCLEOD, D.S., KOENEN, K. C., MEYER, J. M., LYONS, M. J., EISEN, S., TRUE, W., & GOLDBERG, J. (2001). **Genetic and environmental influences on the relationship among combat exposure, posttraumatic stress disorder symptoms, and alcohol use.** *Journal of Traumatic Stress, 14,* 259-275.
Used structural equation modeling to examine genetic and environmental influences on combat exposure, PTSD symptoms, and alcohol use. Analyses were most consistent with a shared vulnerability model for the association between PTSD and alcohol use.

RADANT, A., TSUANG, D., PESKIND, E. R., MCFALL, M., & RASKIND, W. (2001). **Biological markers and diagnostic accuracy in the genetics of posttraumatic stress disorder.** *Psychiatry Research, 102,* 203-215.
Discusses obstacles to the genetic analysis of PTSD, and suggests that these obstacles can be overcome by performing genetic analysis of traits associated with PTSD, e.g., alterations of the HPA axis and increased startle response.

SEEDAT, S., NIEHAUS, D.J., & STEIN, D. J. (2001). **The role of genes and family in trauma exposure and posttraumatic stress disorder.** *Molecular Psychiatry, 6,* 360-362.
Summarizes evidence from family and genetic studies of PTSD. The authors mention issues to be considered in interpreting this literature and suggest that future research delineate the heritability of factors for trauma exposure versus factors for PTSD.

YEHUDA, R., SCHMEIDLER, J., GILLER, E.L., SIEVER, L.J., & BINDER-BRYNES, K. (1998). **Relationship between posttraumatic stress disorder characteristics of Holocaust survivors and their adult offspring.** *American Journal of Psychiatry,* 155, 841-843.
Examined PTSD and trauma in 22 Holocaust survivors and their adult children ($n = 22$). Having a parent with PTSD was associated with increased risk of PTSD following traumatic exposure in the children.

PILOTS UPDATE

Some important changes are coming to the PILOTS Database.

When the National Center was founded in 1989, one of its first projects was the development of a comprehensive bibliographic database that would index the worldwide PTSD literature. Over the fourteen years since then, the PILOTS Database has evolved into the world's foremost gateway to the traumatic stress literature. As the database grew, we have consistently sought to improve users' access to it.

In the Spring 1991 issue of the *PTSD Research Quarterly* we announced that "the first 1,950 PILOTS records are now searchable as the PTSD subfile of the Combined Health Information Database, File CHID on the BRS Search Service." This was not an optimal arrangement. CHID was designed to index patient-oriented literature rather than material written for researchers and clinicians. To search PILOTS one needed a BRS account and password, or access to a library that had one. Searchers paid to use the database. (The National Center did not receive any of this money, and in fact had to pay a substantial fee to subsidize the service.) And the search interface was not exactly user-friendly. But the database was available to people outside the National Center, and it began to attract users. Meanwhile, we were working on improving access to PILOTS.

The Fall 1992 *PTSD Research Quarterly* contained a special four-page pullout section, "PILOTS on Dartmouth: A guide to using the PILOTS Database on the Dartmouth College Library Online System." With this "user-friendly way of searching the traumatic stress literature," we proudly announced, "no password is required, and there is no fee for search time or for citations retrieved. All you need is a computer, a modem, a telephone line, and a communication program."

Like BRS, DCLOS provided a command-based textual interface. (In fact, it was powered by the same search engine.) But its command structure was much easier to use than CHID's; it was designed for students rather than librarians; and it cost the searcher nothing to use, so there was no financial penalty for sloppy typing or badly conceived search strategies. It served its users well, and when DCLOS was withdrawn from service in December 2002 there were many who regretted its passing.

Dartmouth College has always been at the forefront of academic computing, and so it is hardly surprising that Dartmouth was an early adopter of the graphical approach to database searching. In Fall 1997 the Dartmouth College Information System, originally limited to on-campus use, began to offer access to library catalogs and databases on the Dartmouth website, and among these databases was PILOTS.

For more than a decade the PILOTS Database and its users have benefited from the National Center's association with Dartmouth College and its libraries. However, recent developments in academic computing are bringing that relationship to an end. Like most libraries, Dartmouth is moving away from mounting databases on its own computers and instead moving toward to licensing access to those databases on external websites. We have been informed that Dartmouth will soon discontinue its use of the BRS Search software that makes searching the PILOTS Database possible. We shall have to find a new host for the database, and PILOTS users will have to learn some new searching procedures.

We have identified an online database publisher with whom we are working to provide a new home for the PILOTS Database, and we are currently sorting out the technical details of making our data compatible with their software. By the time this column is in print we expect to have begun beta testing the new version of the database. And in next issue's "PILOTS Update" we intend to describe it in some detail.

Our hope is that the new version of the PILOTS Database will offer not only continued access to the traumatic stress literature but also substantial improvements to search capabilities. As we approach our 25,000th record, we mean to continue the progress we have made over the past dozen years in improving access to the Published International Literature On Traumatic Stress from which we take our name.

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